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R. Temple, ... , J. Robbins, J. Wolff

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Research Article

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Neither inhibition of release nor of hormone disappearance seemed to be affected by methimazole (release: 52% decrease without methimazole, 60% with methimazole; hormone disappearance: ~60% decrease in both). When Li^+ was discontinued, recovery of the iodine release rate and hormone disappearance rate over the observed time span was variable, ranging from no recovery to rates that exceeded pre- Li^+ values.

When Li^+ is used alone its effect on serum hormone levels is diminished due to continued accumulation of iodide by the thyroid. Thus, serum thyroxine-iodine levels fell 21-30% in 6-8 days in patients who did not receive methimazole and 15-67% in the methimazole-treated subjects. [...]

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The Use of Lithium in the Treatment of Thyrotoxicosis

R. TEMPLE, M. BERMAN, J. ROBBINS, and J. WOLFF

From the Clinical Endocrinology Branch and Mathematical Research Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

ABSTRACT Since lithium has been shown to inhibit release of iodine from the thyroid, we have investigated its therapeutic potential in thyrotoxicosis. Eight detailed ^{131}I kinetic studies were performed on seven thyrotoxic women and data was analyzed using a computer program. Lithium at serum levels of about 1 mEq/liter decreased the loss of ^{131}I from the thyroid, led to a fall in serum ^{131}I levels and diminished urinary ^{131}I excretion. Computer simulation of the lithium effect required, in every case, that lithium inhibit hormonal and nonhormonal thyroid iodine release. In five cases a second lithium effect was required for a satisfactory fit of the model solution with observed data: namely, an inhibition of hormone disappearance from serum.

Neither inhibition of release nor of hormone disappearance seemed to be affected by methimazole (release: 52% decrease without methimazole, 60% with methimazole; hormone disappearance: \sim 60% decrease in both). When Li^+ was discontinued, recovery of the iodine release rate and hormone disappearance rate over the observed time span was variable, ranging from no recovery to rates that exceeded pre- Li^+ values.

When Li^+ is used alone its effect on serum hormone levels is diminished due to continued accumulation of iodide by the thyroid. Thus, serum thyroxine-iodine levels fell 21–30% in 6–8 days in patients who did not receive methimazole and 15–67% in the methimazole-treated subjects. For prolonged therapy, therefore, a thiocarbamide drug must be used in conjunction with Li^+ . The similarity of inhibition of iodine release from the thyroid produced by Li^+ and iodides is discussed.

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All correspondence should be addressed to Dr. J. Wolff at NIH.

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INTRODUCTION

Although lithium (1) salts have been used to treat manic-depressive psychoses since 1948 (2), it was only in 1967 that goiter was noted in some of these patients (3). Investigation of the mechanism of goitrogenesis suggested that lithium ion blocks the release of iodine from thyroid gland without significantly impairing other aspects of thyroid function. This was first proposed by Sedvall (4) who observed a prolonged thyroid ^{131}I half-life in a patient with normal ^{131}I uptake. In rats chronically treated with lithium (5) the rate of release of thyroid ^{131}I was reduced by as much as 80% and this was accompanied by the gradual development of small goiters. Other parameters of iodine metabolism were not markedly affected or were stimulated.

Antithyroid agents which block organification of inorganic iodine produce clinical relief of hyperthyroidism only after thyroid iodine stores are depleted, and this depletion may take many weeks to occur (6, 7). The only therapeutic agents that inhibits release of thyroid hormone directly is inorganic iodine, but problems created by its use include interference with a number of diagnostic measurements of thyroid function, a significant incidence of poor response or even exacerbated thyrotoxicosis (8), and delay of ^{131}I therapy. We therefore investigated Li^+ as a potential therapeutic agent in patients in whom a prompt decrease in thyroid hormone levels is required (1). While these studies were in progress, Burrow, Burke, Himmelhoch, Spencer, and Hershman (9) reported that lithium administration slowed the loss of ^{131}I from the thyroid glands of two thyrotoxic patients.

METHODS

Subjects

Seven thyrotoxic patients were referred to us by Washington area physicians. (We thank Doctors Larry Anderson,

TABLE I
Clinical Data in Patients Studied*

Subject	Age	Duration of illness	Time off thiocarbamide therapy at start of study	Estimated gland size	Mean sleeping pulse during week before lithium	Prelithium BMR	Prelithium peak ¹³¹ I uptake	Eye disease
	yr	yr		g		%	%	
Ba. J.	27	0.67	No Rx	30	95	+10	33	—
Br. J.	17	2	27 days	70	100	+31	83	—
G. F.-1	40	1.5	No Rx	80	84	+74	82	—
A. T.	32	5	13 days	80	95	+63	78	+
G. V.	46	2	15 yr	60	106	+10	48	—
D. B.	18	2	13 days	40	74	+49	58	—
H. B.	39	1	6 days	60	89	+46	73	—
G. F.-2†	40	2	56 days	80	—	—	67	—

* For all patients: T₄I was elevated (except in Ba. J.), free T₄ was elevated (except in Ba. J.), anti-thyroglobulin antibodies were absent, cholesterol was normal or low, thyroxine-binding globulin was normal.

† Patient G. F. was studied twice.

Alice Brigham, Mason Robertson, Jay Shapiro, and Aryangat Sukamara for these referrals.) With one exception (G. V. had a widened mediastinum of uncertain etiology) they were found to be free of other significant illness, and were felt to be able to tolerate the delay in beginning established antithyroid therapy that was required for the study. All patients were females with diffusely enlarged thyroids; their clinical features are summarized in Table I. Those subjects who had been treated with thiocarbamide drugs before the study had not yet had a satisfactory response. All antithyroid therapy was discontinued for at least 6 days before the onset of the study. One patient was studied twice.

Procedures

Prestudy evaluation. All patients received a general physical and laboratory examination, and their thyroid status was evaluated with measurements of serum thyroxine-iodine (T₄I),¹ free thyroxine (T₄), antithyroglobulin antibodies, thyroxine-binding globulin, cholesterol, and basal metabolic rate (BMR). Triiodothyronine (T₃) was measured by radioimmunoassay through the generosity of Dr. Reed Larson (University of Pittsburgh). The prestudy data are summarized in Table I. Because of the known antimania effects of lithium, a detailed psychiatric evaluation, with particular attention to mood parameters, was performed on several patients before and during lithium administration.

Study protocol. The study was initiated by the i.v. injection of 200–300 μCi of carrier-free Na-¹³¹I (except for G. F.-2 who received oral Na-¹³¹I). The ¹³¹I content of the thyroid gland, serum, and urine was then measured frequently for the next 24–36 hr. After this period, measurements were made about once per day except for the period after lithium therapy was begun, when their frequency was again increased for 24–36 hr. Thyroid gland ¹³¹I activity was determined with a shielded 2 × 2 inch NaI crystal at a distance of 18 cm from crystal to radiation source. All measurements were compared to standards prepared from a

¹ Abbreviations used in this paper: BMR, basal metabolic rate; MMI, methylmercaptoimidazole; T₃, triiodothyronine; T₄, thyroxine; T₄I, thyroxine iodine.

portion of the sample used for injection. For thyroid gland counting, the standard was placed in a plexiglass phantom. Serum and urine samples were counted in a well-type scintillation counter, generally to a counting error of 3% or less. In several patients (H. B., A. T., D. B., G. F.-1 and G. F.-2) this counting error was reached for the entire study, while in the others, somewhat higher counting errors (5–8%) had to be accepted after 15–20 days. As a rule, serum specimens were obtained at the same time each morning. After total serum ¹³¹I was measured, each specimen was precipitated and washed two to three times with cold 10% trichloroacetic acid and the protein-bound ¹³¹I was counted after dissolving the precipitate in 1 N NaOH. Urine was collected for 6, 12, or 24-hr intervals, and a portion was counted. ¹³¹I excretion is expressed as the amount that would have been excreted in 24 hr if the 6 or 12 hr rate had been maintained, and the value is plotted at the middle of the collection period. The creatinine content of 24-hr urine specimens was measured to monitor the completeness of collections.

Serum thyroxine iodine by column (10) and cholesterol were measured three times a week; BMR was measured twice a week, using a Sanborn model 10 "Metabulator"; free thyroxine (performed by BioScience Laboratories, Van Nuys, Calif. [11]) and thyroxine binding globulin (performed by BioScience) were measured weekly. The resting pulse was taken at least once per night. In four studies, methimazole (methylmercaptoimidazole) (30 mg each 6 hr) was begun 1–5 days after ¹³¹I administration and was continued until the study was completed.

For several days before the start of lithium administration, lactose placebos were given every 8 hr. When rapid changes in the kinetic curves had ceased, lithium carbonate was substituted for the lactose placebo without the patient's knowledge. Serum Li⁺ levels were then measured daily by atomic absorption spectrometry. Generally, the initial dose of lithium carbonate was 600 mg, which yielded a serum level of about 0.5 mEq/liter 8 hr later. Subsequently, 900–1500 mg per day (given in three or four doses) was required to maintain serum lithium levels of 0.6–1.20 mEq/liter. For most studies a stable Li⁺ concentration of about 1 mEq/liter was sought. After the lithium period placebo

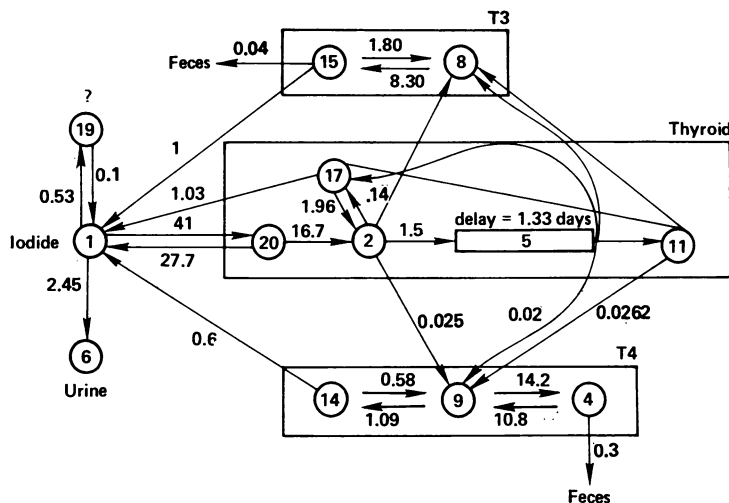


FIGURE 1 Modified ^{131}I kinetic model used in the present analysis. The thyroid, T_3 and T_4 subsystems are depicted in rectangular boxes while individual compartments (comp.) are represented in circles. Rate parameters are those used for Br. J. in the present study. In addition to the exposition of the model given previously (12-14) the following changes and assumptions should be noted: (a) Three new compartments are introduced: 17, which represents intrathyroidal iodide recirculation; 20, which represents the iodide trap; and 19, which is a small, undefined pool of extrathyroidal, possibly organic iodine. It was necessary to introduce compartment 19 to satisfy the early iodide disappearance phases, especially from the point of view of conservation of administered activity. Its physiological significance, if any, is not clear. (b) Intrathyroid deiodination paths going to compartment 17 equal a constant times the sum of the paths from thyroid to extrathyroidal T_3 and T_4 (i.e., hormone secretion). In the non-MMI treated patients the magnitude of this constant could not be resolved and was set = 3.67. (c) Thyroid measurement = $1 \times$ thyroid content + $0.05 \times$ comp 1 + $0.03 \times$ extrathyroidal T_3 and T_4 (except for compartment 4, which is considered to be liver T_4). (d) Thyroid $\rightarrow T_3$ paths are $\frac{1}{2}$ of thyroid $\rightarrow T_4$ paths. There is considerable correlation between the T_3 path and the iodide release path. (e) Early serum data are used in fitting to the model but are not shown in Figs. 2-5. (f) T_4 measurement = comp 9/volume 9. (g) Plasma equivalent spaces: comp 8 = 17.2% of body weight; comp 9 = 4.08% of body weight. (h) Lithium effects. Thyroid: same factor applied to the following thyroid rate constants:

$$\begin{aligned} &L_{0,2}, L_{0,5}, L_{0,11} \\ &L_{8,2}, L_{8,5}, L_{8,11} \\ &L_{17,2}, L_{17,5}, L_{17,11}, \end{aligned}$$

where $L_{i,j}$ is rate constant *into* compartment i from j (units: day^{-1}). Peripheral hormones: same factor applied to deiodination pathways: $L_{1,14}$ and $L_{1,15}$.

administration was resumed while kinetic and other studies continued for another 1-2 wk.

Analysis of data. The kinetic data were analyzed using a general model of iodine metabolism (Fig. 1) modified from Berman et al. (12-14) and the digital computer program SAAM/25, the latest of the SAAM series (15). Beginning with a set of initial estimates for the rate constants $L_{i,j}$ (designated $\lambda_{i,j}$ in previous papers [12, 14]), the computer iteratively adjusted their values until a least squares fit of all the data for a particular study was obtained. Certain of the rate constants were allowed to change during the period of lithium administration and again during

the period after lithium treatment. The general approach was to determine whether adjustment of a single parameter during lithium administration was sufficient for a satisfactory fit to the data, and whether failure to adjust that parameter would result in a poor fit even with all other parameters free to adjust (necessary condition). As will be seen, in some cases adjustment of a single parameter was sufficient, while in others, a second, extrathyroidal effect of Li^+ had to be introduced to account for the data. This second site of action would not have been detected without use of the model, and these results have suggested further studies.

The model (Fig. 1) provides for secretion of hormonal and nonhormonal I from several compartments (12-14), but we did not find it necessary to introduce different lithium effects for each compartment (see legend to Fig. 1). The effect is therefore expressed by a single rate constant for total iodine secretion: the total fractional thyroidal iodine release rate, L_T .

For any compartment i , with content M_i , the secretion of iodine into compartment j is $M_i \cdot L_{j,i}$. Thus, total thyroxine secretion (R_{T_4}) is:

$$R_{T_4} = L_{9,2}M_2 + L_{9,5}M_5 + L_{9,11}M_{11}.$$

Dividing by the total intrathyroidal iodine pool, M_T (where $M_T = M_2 + M_5 + M_{11} + M_{17} + M_{20}$), yields the fractional release rate of thyroxine, L_{T_4} :

$$L_{T_4} = \frac{R_{T_4}}{M_T}.$$

Similarly, for triiodothyronine, the fractional release rate is:

$$L_{T_3} = \frac{L_{8,2}M_2 + L_{8,5}M_5 + L_{8,11}M_{11}}{M_T}.$$

The fractional release rate of iodide is similarly derived. Because iodine initially secreted as iodotyrosine is very quickly converted to iodide, iodotyrosine-iodine is treated as part of the iodide compartment:

$$L_{I^-} = \frac{L_{1,20}M_{20} + L_{1,17}M_{17}}{M_T}.$$

Finally, the total fractional thyroidal iodine release rate is $L_T = L_{T_4} + L_{T_3} + L_{I^-}$. A detailed description of the revised model will be published elsewhere by M. Berman.

RESULTS

Patients with no organification block. Figs. 2 and 3 show kinetic data from two of the four patients who received lithium without methimazole; they illustrate features common to all of these patients as well as some of the variations observed in different studies. After lithium administration there was an abrupt decrease in the rate of loss of thyroidal radioactivity and the decrease persisted throughout the period of Li^+ treatment. However, the thyroid release curves showed marked variation upon cessation of lithium therapy. The rate of loss increased to nearly its prelithium rate in one case, changed little in two cases (e.g., Fig. 3) and increased, but not to its prelithium rate, in the fourth (Fig. 2).

Upon initiation of Li^+ treatment, serum and urine ^{131}I values fell from their pretreatment plateau values. These changes are consistent with, but do not prove, a decrease of ^{131}I release from the gland. In three of the four patients the urinary ^{131}I excretion fell more rapidly during the first 48-72 hr of lithium treatment than did serum ^{131}I levels; subsequently, the two values decreased at nearly comparable rates. The urinary ^{131}I derives from both peripheral breakdown of thyroid hormones and direct thyroidal secretion of iodide. The component arising

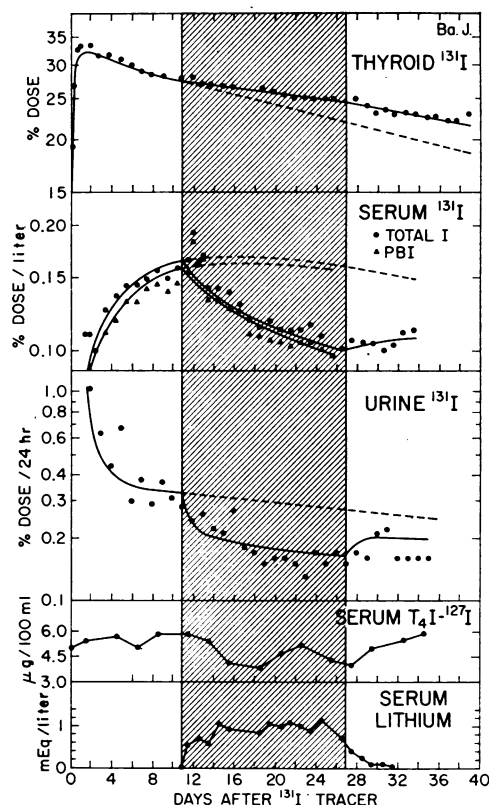


FIGURE 2 ^{131}I kinetics, serum T_4I and serum Li^+ for patient Ba. J. At time zero $Na^{131}I$ was given intravenously; the shaded area is the period of lithium administration. Solid circles and triangles represent measured data while solid lines in the three upper sections of the figure are the computer-generated least squares solutions, assuming that lithium affected only iodine release. The dashed line is the computer-generated description of the behavior of the curves if lithium had not been given.

directly from secretion would be expected to fall rapidly after any interference with secretion and the rapid early fall of urinary ^{131}I reflects this. Serum ^{131}I levels, representing mainly hormone iodine, decay slowly even after an abrupt decrease in secretion. The portion of urinary iodide derived from serum ^{131}I declines in parallel with it. In three of the four studies (the exception is Br. J., Fig. 3) discontinuation of lithium treatment led to increased urinary ^{131}I excretion and serum ^{131}I levels.

The kinetic data were analyzed as described in Methods. The least squares fits are drawn in solid lines in the figures, whereas the dashed lines represent the behavior of ^{131}I that would have occurred without Li^+ therapy in these patients. For Ba. J. (Fig. 2), who was mildly thyrotoxic on the basis of nonsuppressible ^{131}I uptake and elevated T_3 , the data could be fitted, with an acceptably small error (solid line, Fig. 2), by assuming that the only effect of lithium was on total ^{131}I release (L_T) from

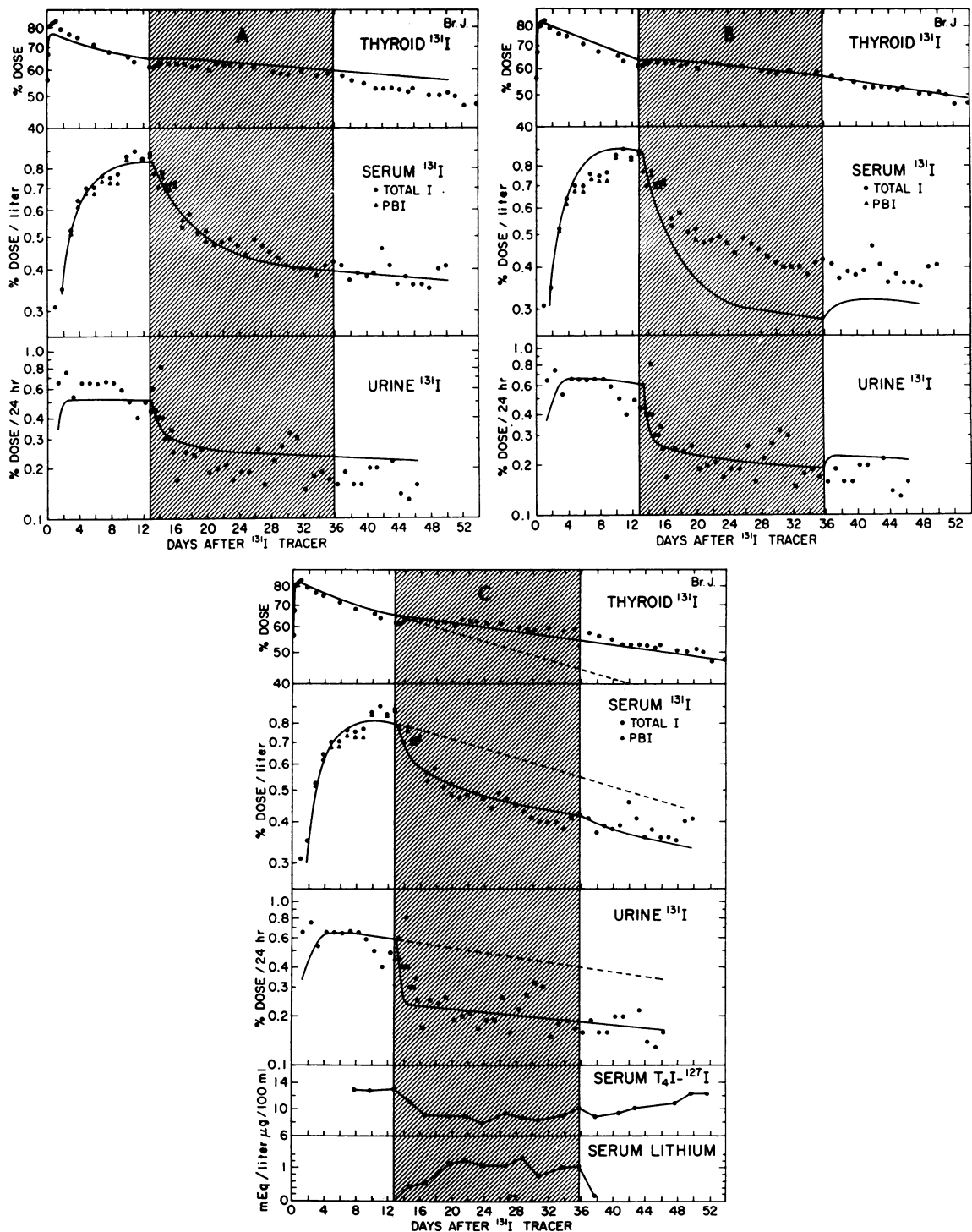


FIGURE 3 Comparison of computer solutions assuming different lithium effects, for patient Br. J. $\text{Na-}^{131}\text{I}$ was given intravenously at time zero; the shaded area is the period of lithium administration. Solid circles and triangles represent measured data in 3A, 3B, and 3C. Solid lines (the $\text{PB-}^{131}\text{I}$ line is omitted) are computer-generated least squares solutions generated under the following assumptions: 3A, lithium affected only iodine release; 3B, lithium affected only iodine release and no weight in the computer solution is to be given to serum data (that is, the curve is fitted only to thyroid and urine data); 3C, lithium affected both iodine release and hormone disappearance. The broken lines in 3C are the description of the behavior of the curves if lithium had not been given.

TABLE II
Fraction of Pretreatment Total ¹³¹I Release Rates (L_T) and T₃ + T₄ Deiodination Rate Attained during and after Li⁺ Therapy

Patient	Methimazole treatment	Pretreatment release rate (L _T) fraction/day	Fraction of pretreatment rates*			
			On lithium		After lithium‡	
			Release	T ₃ + T ₄ deiodination	Release	T ₃ + T ₄ deiodination
Ba. J.	—	0.026	0.52	0.85	0.70	0.85
Br. J.	—	0.098	0.37	0.30	0.37	0.35
G. F.-1	—	0.137	0.33	0.25	0.60	0.30
A. T.	—	0.098	0.70	0.95	1.60	1.80
G. V.	+	0.013	0.40	0.60	0.65	0.60
D. B.	+	0.058	0.15	0.40	0.25	0.45
H. B.	+	0.031	0.70	1.00	§	
G. F.-2	+	0.170	0.35	0.50	1.40	1.40

* These values are calculated on the basis of 1.00 for the pretreatment values. They may be converted to per cent inhibition by $(1.00 - \text{fraction}) \times 100$.

‡ Recovery values are rough estimates. See text.

§ A skin rash required discontinuation of methimazole shortly after lithium was stopped.

the gland, a decrease of 47%. A slightly better fit could be obtained by assuming that lithium also caused a decrease in the fractional rate of disappearance of T₄ from the serum. The best fit in this case (Table II) corresponds to a 48% inhibition of thyroid ¹³¹I release and a 15% decrease in fractional T₄ disappearance rate. Changes in parameter values of as little as 15% cannot be resolved definitely from these data so that either solution can be considered consistent with the observed kinetic curves. The kinetic parameters did not return to their original values when lithium was discontinued, the iodine release rate reaching only 70%, and the T₄ disappearance rate remaining 85% of the pretreatment rates. The effect of lithium therapy is strikingly shown by the dashed lines which simulate the ¹³¹I kinetics that would have occurred in the absence of Li⁺ therapy.

A more striking effect of Li⁺ is seen in Br. J. who was severely thyrotoxic (Table I). The abrupt change in neck counts, the diminution of urinary ¹³¹I excretion, and the fall of serum total and protein-bound ¹³¹I are more impressive than in the study of Ba. J. In contrast to Ba. J. (Fig. 2), the data could not be fitted by assuming that lithium affected a single parameter (total ¹³¹I release rate). If parameters were adjusted to fit the serum data (Fig. 3A) marked deviations between the model (solid lines) and the data occurred in both the urine and thyroid curves. When, on the other hand, they were adjusted to fit the thyroid data, a reasonable fit to the observed urine data could be obtained, but satisfactory matching of the serum kinetic curve could not be achieved (Fig. 3B). Since the fit of the data before Li⁺ treatment

was satisfactory, it seemed that the deviations in the serum curve resulted from the Li⁺ therapy. The too rapidly falling serum curve suggested, furthermore, that if the serum ¹³¹I disappearance were decreased a better fit might be obtained. Introduction of a factor to correct for the extent of the deviation in serum ¹³¹I yielded much improved fits (Fig. 3C). Moreover, the post-Li⁺ recovery showed an improved fit as well.

It is of considerable interest that while a Li⁺ effect on release was anticipated from our rat studies (5) and would be consistent with the neck counts in these patients, an effect on T₄ disappearance from the serum was not expected from the rat data and was not observed in one case of thyrotoxicosis.² For these reasons T₄ disappearance studies were not performed in our patients. The rigorous testing of the model, however, required this additional locus of lithium action. The effect on disappearance could be due to changes in one of the following: fecal excretion rate, thyroxine space, or degradation rate. Since the higher serum ¹³¹I is accompanied by diminished loss of radioactivity in the urine (e.g., Fig. 3A), it seems reasonable to ascribe this second Li⁺ effect to decreased deiodination. In our modeling, therefore, the lithium effect on T₄ disappearance has been placed in the deiodination pathway (L_{1,14}) and we have left the rate of fecal losses unaltered (L_{1,100,1}). This is not meant to suggest that the latter parameter could not be affected; only that we did not need to introduce any change to obtain the quality of fit shown.

² Dr. R. S. Bernstein, St. Louis, Mo. Personal communication.

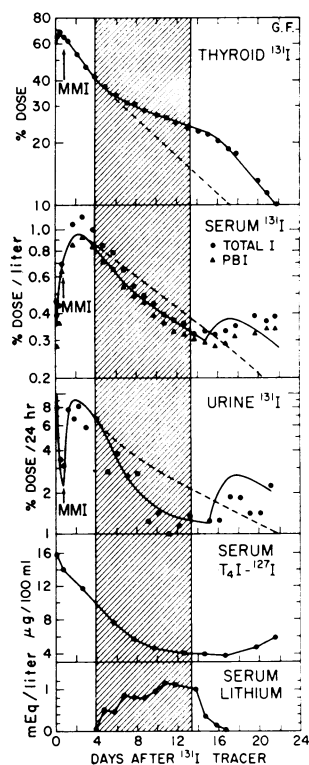


FIGURE 4 ^{131}I kinetics, serum T_4I , and serum Li^+ for patient G. F.-2. At time zero Na^{131}I was administered orally; the shaded area is the period of lithium administration. Arrows mark the start of methimazole treatment at 30 mg each 6 hr. Solid circles and triangles are data points; solid and dashed lines have the same meaning as in Fig. 2; the $\text{PB-}^{131}\text{I}$ line is omitted.

It should be pointed out that even with this improved fit the model shows two areas of discrepancy with the data. Both of these occur during periods of changing Li^+ concentration (i.e., onset and cessation of therapy). Although no attempt was made to develop a dose response curve for the lithium effect, changes in the rate of ^{131}I loss from the gland and in the rate of urinary ^{131}I excretion could be detected in all patients within 24 hr after the first lithium dose. At that time the serum lithium was never more than 0.5 mEq/liter, which can thus be taken as an upper limit for the minimum effective dose. However, a full Li^+ effect was probably not attained at this time and, since the model assumed an instantaneous Li^+ effect, the early deviations may be due to this approximation.

The other two patients, A. T. and G. F.-1, who were treated with Li^+ alone, showed essentially similar responses in their iodine kinetics. In A. T. a relatively small effect was obtained (Table II) and changes in degradation rate were not acquired to obtain a good fit of the data to the model. The poor response may be due

to the fact that Li^+ levels hovered around 0.6 mEq/liter. The study of G. F.-1 gave results rather similar to those of Br. J., except that during the second week of lithium therapy there was a diminution of the lithium effect associated with a fall in serum lithium from about 1.0 mEq/liter to 0.6 mEq/liter. Recovery of the kinetic parameters was variable. A. T. showed a return to normal of all ^{131}I parameters when the serum Li^+ had declined to < 0.1 mEq/liter, whereas G. F.-1 showed an incomplete return to the pretreatment rate of loss of ^{131}I from the thyroid (Table II).

Patients with organification block. Since the slopes describing thyroid ^{131}I loss and urinary ^{131}I excretion are markedly damped by recirculation of radioisotope, four studies were performed in the presence of large doses of methimazole in order to reduce uptake parameters toward zero, and enhance the changes in slope due to lithium.

Two of these studies are presented in Figs. 4 and 5. Methimazole therapy was associated in all cases with a prompt increase in the rate of thyroid ^{131}I loss, as was expected from the inhibition of recirculation of iodide. Lithium promptly diminished this rate of loss in all four patients. Although the onset of the Li^+ effect was prompt (Figs. 4 and 5), the rate decreased further after several days of treatment. In D. B. this may have been related to somewhat higher serum lithium levels. This behavior is like that seen in some of the patients not simultaneously treated with methimazole.

Serum ^{131}I levels were allowed to plateau before Li^+ treatment was begun. In G. F.-2 the methimazole period was shortened because of severe thyrotoxicity. With lithium administration, serum ^{131}I began to decline and continued to do so, although at a decreasing rate, until the lithium was discontinued, at which time it either stabilized at about 40–50% of the prelithium values (Fig. 5) or rose slightly (Fig. 4).

Urinary ^{131}I excretion, which was dramatically increased by methimazole in all patients, fell very rapidly for 2–3 days after the onset of lithium treatment, as it had in three of the four studies without methimazole. It then continued to fall roughly in parallel with the serum values until lithium treatment was stopped, at which time there was a slight, short-lived rise.

In this group of patients the inhibition of thyroid ^{131}I release produced by Li^+ treatment varied from 30–85% (Table II). In order to fit the observed data, it was again necessary to introduce a second effect of Li^+ on the iodine kinetics, namely an inhibition of peripheral hormone disappearance. In the cases of D. B. and G. F.-2 the serum ^{131}I deiodination rate was reduced 60% and 50%, respectively. In one of the two other patients of this group (H. B.) Li^+ had no effect on T_4 disappearance, whereas in the fourth (G. V.) there was a re-

duction in deiodination of 40% (Table II). The extent of the Li^+ effect upon the three kinetic curves is again indicated by the dashed lines which portray the behavior of the model that would occur in the absence of a Li^+ effect (Figs. 4 and 5).

A summary of the effects of Li^+ on those kinetic parameters which exhibit the major changes during treatment is given in Table II. It is apparent that there are wide variations in the response of both the total ^{131}I release rate and the peripheral deiodination rate. In fact the model solution did not require a significant effect of Li^+ on extrathyroidal iodine metabolism in three of the eight cases.

It seems probable that methimazole does not have a marked effect on either parameter change, since the mean inhibition of release was 52% and 60%, and of $\text{T}_3 + \text{T}_4$ disappearance was 59% and 62% for untreated and methimazole-treated patients, respectively. However, it is not yet possible to say this with certainty. Whether or not the Li^+ effect on the two parameters is linked (as is suggested by the poor response in both patients A. T. and H. B.) requires further study.

The return toward pretreatment rates of these kinetic parameters upon cessation of Li^+ therapy is also listed in Table II. These values are rough indications, since the mechanism to explain inconsistencies in that region of the data has not yet been worked out. Again there is a wide spectrum of response. Br. J. showed little recovery in either parameter, whereas A. T. and G. F.-2 attained values exceeding the pretreatment rates. It appeared that ^{131}I release from the thyroid returned toward normal rates more often than did the thyroxine deiodination rate, but more data are needed before this can be stated with any assurance.

Effect on serum ^{131}I -hormone levels. The effect of lithium given with and without methimazole on the serum T_4I is summarized in Table III. In the unblocked patients there was a 25–32% decrease in T_4I within 4–5 days, after which there was essentially no further fall, even though the $\text{PB-}^{131}\text{I}$ continued to decline. When lithium was discontinued, there was a rapid (within 4 days) return of the serum T_4I to pretreatment levels in three of the four patients. The exception was Br. J. (Fig. 3C) in whom this return took about 2 wk.

Methimazole-treated patients had a more striking fall (23–59% in 4–5 days) of serum hormone levels, three of four reaching a normal serum T_4I 4–5 days after the start of lithium (the exception, G. V., fell to the upper limit of normal at 10–11 days, despite her failure to respond to 2 months of treatment with high doses of methimazole). In contrast to the unblocked patients, hormone levels continued to fall with continued lithium administration. In addition, the rapid postlithium recovery of serum T_4I

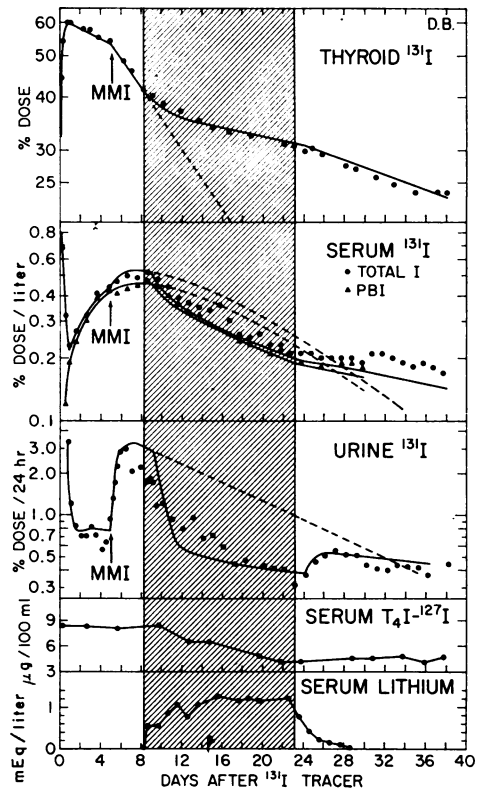


FIGURE 5 ^{131}I kinetics, serum T_4I , and serum Li^+ for patient D. B. At time zero Na^{131}I was given intravenously. The shaded area is the period of lithium administration and arrows mark the start of methimazole treatment at 30 mg each 6 hr. Solid circles and triangles are data points; solid and dashed lines have the same meaning as in Fig. 2.

levels did not occur (Figs. 4 and 5), hormone levels rising only slightly.

Serum T_3 levels were measured before and after lithium administration in five patients, and appeared to fall somewhat more than the T_4 levels (Table III). Because of more rapid disappearance rates the T_3 levels might be expected to fall more rapidly. Studies of early T_3 changes are now in progress.

Clinical changes. The clinical response to lithium correlated in general with the changes of serum T_4I levels (Table III). Thus the four patients treated with lithium alone and G. V., of the lithium-methimazole group (only two of whom, Br. J. and G. F.-1, were very symptomatic), had only small changes toward normal. In Br. J., who had the greatest T_4I response of that group, a fall in resting pulse (100–86) and BMR (+31–+19) was demonstrated. The greater fall in serum hormone levels in three of the four patients treated with both lithium and methimazole corresponded with a more impressive clinical response, when this could be evaluated. D. B., who was quite symptomatic, became wholly free of symp-

TABLE III

Serum Thyroxine Iodine and Triiodothyronine Changes after Lithium Therapy

Patient	Days on methimazole before Li ⁺	Pre-Li T ₄ I* (mean of several)	T ₄ I			T ₃ ‡	
			Days on Li ⁺			Pre-Li ⁺	10-14 days on Li ⁺
			4-5	6-8	10-11		
		μg/100 ml	μg/100 ml	μg/100 ml	μg/100 ml	ng/ml	ng/ml
Ba. J.	—	5.5	4.1 (25)§	3.8 (31)	4.7 (15)	3.1	1.9 (39)
Br. J.	—	13.5	9.2 (32)	9.1 (33)	8.0 (41)	5.0	2.4 (52)
G. F.-1	—	15.4	10.4 (32)	11.4 (26)	10.2 (34)	7.3	3.6 (51)
A. T.	—	13.2	—	9.9 (25)	9.3 (30)	5.0	3.0 (40)
G. V.	7.6	9.2	—	7.8 (15)	6.6 (28)	3.1	2.5 (19)
D. B.	3.3	8.4	6.5 (23)	—	4.7 (44)	—	—
H. B.	5.3	10.0	4.8 (52)	4.6 (54)	—	—	—
G. F.-2	3.1	13.8	5.7 (59)	4.6 (67)	3.9 (72)	—	—

* Normal 3.1–6.7 μg/100 ml.

‡ Normal 0.6–1.6 ng/ml.

§ The values in parentheses represent the per cent fall from prelithium levels during lithium therapy.

toms and also had a significant fall in pulse (74–57) and BMR (49–24). H. B. and G. F.-2 also became free of thyrotoxic symptoms, but evaluation was hindered in the former by an upper respiratory infection (pulse and BMR did not fall) and in the latter by the use of propranolol.

In no patient was a change in thyroid gland size noted during the study. Cholesterol levels did not change remarkably in any of the patients. Measurement of free T₄ confirmed changes noted in total thyroxine-iodine values. Thyroxine-binding globulin, antithyroglobulin antibodies, and other laboratory determinations did not change significantly during lithium treatment.

The possibility that lithium produced a calming effect on hyperthyroid patients apart from its antithyroid action was considered, but we were unable to detect such a phenomenon. As part of our attempt to evaluate mental changes the study was double blind for both the patient and the psychiatric staff. Although mild depression was observed in several patients, it was associated with the mild anorexia and nausea that occurred at least transiently in most cases, and could not be interpreted as an independent effect. No evidence of lithium toxicity other than gastrointestinal disturbances was observed; in no case were these symptoms severe enough to require discontinuation of the drug, although in G. F.-1 the dose was reduced because of nausea and vomiting.

DISCUSSION

The present data show that low serum concentrations of lithium ion (0.5–1.0 mEq/liter) lead rapidly to a 30–85% decrease in the secretion of both iodide and hormonal iodine from the toxic human thyroid gland, reflected simultaneously in an increased thyroid ¹³¹I half-life, decreased urinary ¹³¹I excretion, and declining serum ¹³¹I and

serum thyroxine iodine. The decreased secretion rate follows rapidly the attainment of serum lithium levels of 0.5 mEq/liter. The effect of lithium was unaltered when iodination was blocked with methimazole. Our data were compatible with a model that assumed coordinate inhibition by lithium of hormonal and nonhormonal iodine release. Such inhibition suggests decreased thyroglobulin hydrolysis, which would reduce secretion of all thyroglobulin components equally. Recent studies in laboratory animals (16, 17) showing that low doses of lithium given in vivo inhibit in vitro colloid droplet formation in response to TSH or dibutyryl cyclic-AMP, strongly support this interpretation.

An unexpected finding, and one that differed from our rat data (5) and from studies in one thyrotoxic² and several euthyroid³ patients, was that adjustment of a single kinetic parameter, that describing thyroid iodine secretion, was sufficient to account for the changes in the kinetic curves in only three of the eight patients (e.g., Fig. 2 and Table II). In the others a second effect of Li⁺ had to be introduced, i.e., one on T₄ deiodination. These results emerged entirely from the rigorous modeling and data fitting process and direct measurements of a Li⁺ effect on this parameter were not carried out in this study. Ohlin and Söderberg (18) have reported, without accompanying data, a significant decrease in T₄ disappearance rate in the rat, and recent investigations by Carlson³ in thyrotoxic patients and by Burrow⁴ in both normal and hyperthyroid patients have demonstrated changes in

³ Dr. H. Carlson, Bethesda, Md. In preparation.

⁴ Dr. G. N. Burrow, New Haven, Conn. Personal communication. We should like to thank Dr. Burrow of Yale University School of Medicine for making these values available to us before publication.

T₄ disappearance rates following Li⁺ treatment that are entirely in agreement with those presented in Table II.

The decrease in hormone degradation that accompanies the decreased hormone secretion induced by Li⁺ tends to diminish the fall in serum hormone levels. In some patients (e.g., G. F.-1, Br. J.) the changes in the two parameters would appear to cancel one another. The fact that the serum T₄ falls in these patients is consistent with our assumption that fecal T₄ losses are unaffected by lithium, with only losses by deiodination pathways being inhibited. Studies to measure directly the effects of lithium on fecal T₄ losses are currently in progress.

The model does not at present include a pathway for conversion of T₄-¹³¹I to T₃-¹³¹I. With the extent of T₄ to T₃ conversion a matter of controversy at present, inclusion of the pathway would have necessitated selection of wholly arbitrary rate constants and would not have affected our findings of decreased thyroid iodine release and decreased T₄ deiodination. We plan direct exploration of the T₄ to T₃ subsystem in the future, especially with regard to the possibility that lithium might inhibit this conversion.

The present model does not require a lithium effect on iodide uptake. This is in agreement with some studies (9) but contrasts with others in which uptake was decreased (19, 20) or increased (3-5). Increased iodide uptake might accompany lithium-induced goiter caused by low circulating T₄ and T₃ with elevated TSH (3, 5, 9, 21, 22). However, none of the present group of thyrotoxic patients became hypothyroid.

The rigorous testing of the model raised several points that require further investigation and analysis. In addition to the effect on hormone disappearance there also seems to be a delayed effect in the action of Li⁺. This means that instead of plasma Li⁺ some other Li⁺ compartment is probably the important variable to consider. In neglecting these factors the model solution still contains some systematic deviations. It may even be necessary to introduce some time-dependent effects. Until this is investigated in detail and resolved, conclusions about other sites of action of lithium cannot be made with confidence. Hence, the above statements regarding fecal loss and iodide uptake contain an element of uncertainty.

A decreased iodine release rate accompanied by unchanged iodine uptake implies that in unblocked glands, iodine might be expected to accumulate, and such an accumulation has been found in lithium-treated rats (5). The thyroid iodine pools of the lithium-treated patients who did not receive methimazole have been calculated to have increased. This would tend to minimize the fall in serum T₄ in these patients, as was observed (Figs. 2 and 3 and Table III), and may partly explain the rapid rise of hormone levels when lithium was stopped.

Patients treated with methimazole could not accumulate iodine. This may explain the continued fall of serum and the absence of a substantial postlithium rise in T₄I levels.

Except for lithium, iodide is the only agent in clinical use that affects iodine release from the thyroid gland. Iodide decreases ¹³¹I release from previously labeled thyroid glands in Graves' disease in the presence (23-26) or absence (23, 27, 28) of methimazole blockade of uptake. It also inhibits TSH-stimulated release of iodine in experimental animals (29) and normal patients (25, 26). Wartofsky, Ransil, and Ingbar have recently studied the inhibition of thyroxine release by iodine (23). They found in eight patients that the thyroxine release rate was inhibited an average of 72.8% (range 61.2-91.5%), a somewhat greater inhibition than we have demonstrated for lithium. In a striking parallel to the Li⁺ effect, serum thyroxine levels fell only 26-48% and tended to level off in 3.5-6.5 days, whether or not methimazole was used with the iodine.

A further similarity between iodine and lithium is the difficulty in controlling thyrotoxicosis for long periods with either agent. In a recent study, Harden, Koutras, Alexander, and Wayne (30) found that patients with good clinical and T₄ responses to iodide treatment at the end of 2 wk had relapsed by the end of 4 wk despite continued therapy, their T₄ values returning to pretreatment levels. Since iodine accumulates in thyrotoxic glands treated with Lugol's solution (31), we suggest that in patients treated either with iodide (23, 30) or lithium alone, increased glandular hormone content permits total hormone release to rise despite a decreased fractional rate of secretion. This eventually leads to escape from control. Hence the chief use for either agent alone is for short-term, rapid suppression of thyroid secretion. The addition of methimazole or another thiocarbamide drug is necessary to prevent escape from such suppression with prolonged use. Given the uncertainty regarding complete prevention of an iodine leak through methimazole block and the role of iodine as thyroid hormone substrate, lithium appears to be the preferred agent when a rapid inhibition of hormone secretion is required. These considerations must be weighed against the possible toxic effects of lithium and the possibility that the inhibition of T₄ disappearance by lithium may impair its effectiveness in some instances.

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